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Original Research Article

Ameliorative effect of Draba nemorosa extract on chronic heart failure in rats

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Abstract

Purpose: *To evaluate the effect of Draba nemorosa extract (DNE) on oxidative stress and hemodynamics in rats with chronic congestive heart failure (CHF).*

Methods: *Adriamycin was used to establish CHF in Sprague Dawley (SD) rat model. Six groups of SD rats were used in this study: control group, CHF group, captopril group (0.1 g/kg), as well as high-, medium- and low-dose DNE groups (5.2, 2.6 and 1.3 g/kg, respectively). Treatment for all groups lasted 4 weeks. Blood pressure and heart index were measured. In addition, serum creatine kinase (CK), superoxide dismutase (SOD), malondialdehyde (MDA), nitric oxide (NO) and nitric oxide synthase (NOS) were determined with enzyme-linked immunosorbent assay (ELISA) kits.*

Results: *In the CHF group, arterial systolic pressure (SBP, 84.22 ± 16.23 mmHg); diastolic pressure (DBP, 77.36 ± 20.29 mmHg); mean arterial pressure (MAP, 78.45 ± 10.56 mmHg); heart rate (HR, 357.18 ± 37.34 beats/min) and left ventricular systolic peak (LVSP, 102.34 ± 16.37 mmHg) were significantly decreased ($p < 0.05$) when compared with the control group. However, left ventricular end diastolic pressure (LVEDP, 23.38 ± 1.78 mmHg); heart index (2.74 ± 0.16 mg/g); serum CK (0.87 ± 0.15 U/mL); MDA (19.34 ± 2.57 nmol/mL), NO (38.43 ± 3.32 umol/L) and NOS (42.65 ± 3.32 U/mL) were increased. Treatment with high-dose DNE significantly ameliorated hemodynamic function, and reduced MDA (9.13 ± 2.12 nmol/mL) and NO (22.37 ± 3.16 umol/L) levels ($p < 0.05$). High-dose DNE also led to significant decreases in CK (0.53 ± 0.35 U/mL) and NOS (24.27 ± 3.55U/mL) in the CHF rats ($p < 0.05$).*

Conclusion: *DNE significantly improves hemodynamic function in CHF rats. Thus, it has a potential for development into a new drug for clinical treatment of CHF.*

Keywords: *Draba nemorosa, Adriamycin, Chronic heart failure, Hemodynamic function, Oxidative stress*

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INTRODUCTION

Chronic heart failure (CHF) is a consequence of cardiac disorder [1]. The incidence of heart failure (HF) in developed countries for people over 65 years old is about 1 % [2]. It has been shown that the morbidity from HF in ten provinces of China has reached 0.9 % [3]. However, it must be noted that the current prognosis of CHF is far from satisfactory, and therapeutic regimens are limited. To some extent, the situation is much worse for HF than cancer [4]. Furthermore, hospitalization burden and healthcare expenditures make HF a global health issue.

The frequently adopted treatments for HF include angiotensin-converting enzyme (ACE) inhibitors,

β-adrenoceptor blockers, and digitalis [5-7]. Although the guidelines on CHF therapy have been updated by American Heart Association (AHA) and European Society of Cardiology (ESC) [2], HF remains a major cause death [8]. Thus there is need to explore new therapeutic regimens for HF.

The use of Traditional Chinese Medicine (TCM) for treatment of complex, multi-factorial diseases is gaining acceptance. It has been recognized that TCM effectively treats symptoms, reduce side effects and reverse resistance via targeting multiple pathways. TCMs such as *Shengmai* [9], *Sini* decoction [10], *Shuanglong* formula [11], and *Huangqi* injection have been reported to exhibit potential pharmacological activities against cardiovascular diseases [12]. *Draba nemorosa* stimulates blood circulation, thus eliminating blood stasis. It also contributes to replenishment of blood, reduces swelling and relieves pain [13,14]. So far, there are no reports in the literature on the use of *Draba nemorosa* for treating cardiovascular diseases. This study was aimed at investigating the effect of DNE on CHF in a rat model.

EXPERIMENTAL

Materials

Draba nemorosa was obtained from Pingdingshan City, Henan Province of China in May 2015, and identified by Professor Zhi He of Nanjing University, China. A voucher specimen (No. DNE 201505013) was kept at the College of Pharmacy, Jiangsu University of China, for future reference. An aqueous extract of *Draba nemorosa* was prepared and freeze-dried to obtain DNE at a yield of 50 % (2.0 g of *Draba nemorosa* yielded 1.0 g of DNE)

Animals

Healthy male SD rats were purchased from the Experimental Animal Center of Jiangxi Province (Certificate no. SYXK 2005-0004). They were kept in single cages in an atmosphere of temperature 20 ± 2 ^{o}C, and allowed free access to animal feed and clean drinking water. The experiment was approved by the Animal Care and Use Committee of the Second People's Hospital of Huai'an (approval ref no. 20110806). The study was carried out in accordance with Directive 2010/63/EU [15].

Modeling and treatment

The experimental groups consisted of control group, adriamycin-treated CHF group, captopril group (0.1 g/kg), as well as high, middle and low-dose (5.2, 2.6 and 1.3 g/kg, DNE groups, respectively, n = 10). Rats in the control group were administered an equivalent volume of saline in place of adriamycin hydrochloride (2 mg/kg). Adriamycin rat model established via administration of the drug, once a week for 6 weeks.

At the 6th week, 2 rats were chosen and checked for heart failure. The adriamycin administration was extended for a further 4 weeks for rats that had not successfully developed heart failure (untreated rats). Drug administration began from the 7th week of the experiment and lasted for 4 weeks. Except for the administration of saline to the control and adriamycin-induced CHF animals, DNE group received 1.3, 2.6 or 5.2 g/kg DNE once a day intra-gastrically, with 100 mg/kg captopril administrated to the captopril group only.

Determination of cardiac function and hemodynamics

Twenty-four h to the end of the experiment, the rats were anesthetized with 20% urethane solution (6 mL/kg). Then the animals were fixed in a spinal position. Ventricular cannula was used to separate the right common carotid artery using 1.0 % heparin. Parameters concerning cardiac function were determined, and observation of pressure oscilloscope was performed. The advance was stopped when transformation of the wave shape was observed and the pulse pressure significantly was uplifted. The parameters recorded were LVSP, LVEDP, $+dp/dt_{max}$ and $-dp/dt_{max}$. Mean values of the hemodynamic indices were obtained for calculations in 5 sections. Blood samples were thereafter collected from the abdominal aorta. Half of the blood samples were in sodium EDTA bottles, while the other half were without anti-coagulant. All the samples were stored at -20 ^{o}C before analysis.

Measurement of heart index

Heart index (HI) was determined after cardiac function and hemodynamics measurements. The weight of the whole heart was measured, and the heart weight index was calculated as the ratio of whole heart weight (mg) to body weight (g).

Determination of serum biochemical indices

Serum CK, SOD, MDA, NO and NOS were determined using ELISA kits (Shenzhen Xin Bo Sheng Biological Technology Co., Ltd., Shenzhen, China) according to manufacturer's

Statistical analysis

Data are expressed as mean ± standard error of mean (SEM). Statistical Package SPSS 16.0 (SPSS Inc, Illinois, Chicago, USA) was applied for data analysis using one-way analysis of variance (ANOVA) and Dunnett's t-test. Statistical significance was set at $p < 0.05$.

RESULTS

Effect of DNE on heart index

There was a significant increase in HI in the model group when compared with the normal group ($p < 0.05$), which is an indication that myocardial hypertrophy was successfully established in the model group (Table 1). On the contrary, there was no significant variation in HI in the captopril and DNE groups.

Table 1: Effect of DNE on heart index

Group	Dose (g/kg)	HI (mg/g)
Control	-	2.14±0.22*
Untreated	-	2.94±0.15
Captopril	0.1	2.41±0.23
DNE-L	1.3	2.71±0.34
DNE-M	2.6	2.54±0.29
DNE-H	5.2	2.42±0.25

*L, M and H represent low-, medium- and high-doses of DNE, respectively, (n = 10, *p < 0.05)*

Effect of DNE on hemodynamic parameters

There were sharp decreases in SBP, DBP, MAP, LVSP, ± dp/dtmax and HR in the adriamycin-treated CHF group, when compared with control ($p < 0.05$). Significant increases in LVEDP ($p < 0.01$) were observed in the model group relative to the control group, but DNE (high dose) was able to bring about a significant reduction in this parameter. Moreover, DNE led to significant improvement in vasomotoricity and left ventricular function in adriamycin-treated CHF rats ($p < 0.05$), while captopril exhibited very little effect (Tables 2 and 3).

Effect of DNE on serum biochemical indices

There were significant increases ($p < 0.01$) in blood levels of CK, NOS, MDA, and NO levels, and sharp decreases ($p < 0.01$) in activity of SOD in blood of rats in the CHF group, when compared with control. However, captopril administration brought about significant reductions in CHF-induced increases in blood levels of CK, NOS, MDA, and NO ($p < 0.01$), while DNE had no significant effect on SOD activity; Table 4).

DISCUSSION

In this study, cardiac function was assessed by various hemodynamic parameters. The results obtained suggest that diastolic function and contraction could be improved by DNE.

The left ventricular function was appreciably improved without affecting heart rate. It appeared that DNE exhibited higher pharmacological activity than captopril. Heart failure can be induced by oxidative stress [16], since reactive

Table 2: Effect of DNE on hemodynamic indices

Group	Dose (g/kg)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (beats/min)
Control	—	125.45±13.37*	113.43±16.41*	105.28±13.35*	428.24±31.38*
Untreated	—	84.22±16.23	77.36±20.29	78.45±10.56	357.18±37.34
Captopril	0.1	117.25±26.58	93.25±33.47	98.32±25.31	409.33±48.26
DNE-L	1.3	91.43±20.23	82.42±26.35	82.26±16.26	379.39±34.31
DNE-M	2.6	110.34±17.24*	97.27±18.57	94.31±15.42	389.36±28.58
DNE-H	5.2	123.32±13.48**	105.32±21.32**	112.34±12.76**	417.28±38.24*

*L, M and H represent low-, medium- and high-doses of DNE, respectively, (n = 10, *p < 0.05, **p < 0.05)*

Table 3: Effect of DNE on hemodynamic indices

Group	Dose (g/kg)	LVSP (mmHg)	LVEDP (mmHg)	+dp/dt$_{max}$	-dp/dt$_{max}$
Control	—	153.41±12.86*	8.43±1.56**	3745.26±415.53*	3765.35±437.53*
Untreated	—	102.34±16.37	23.38±1.78	2154.16±643.56	2367.34±653.23
Captopril	0.1	115.27±31.48	15.27±2.36	3536.43±818.24	3452.21±706.34
DNE-L	1.3	112.36±19.33	16.34±2.08	2435.32±557.34	2543.45±626.75
DNE-M	2.6	125.17±15.35*	14.28±2.57	3213.25±487.76*	3324.25±532.25*
DNE-H	5.2	138.25±16.22*	11.17±2.33*	3594.31±512.26*	3654.31±515.28*

*L, M and H represent low-, medium- and high-doses of DNE, respectively, (n = 10, *p < 0.05, **p < 0.05)*

Table 4: Effect of DNE on some serum biochemical indices

Group	Dose (g/kg)	CK (U/mL)	SOD (U/mgprot)	MDA (nmol/mL)	NO (umol/L)	NOS (U/mL)
Control	-	0.39±0.13**	96.43±7.26**	6.48±1.65**	18.24±1.84**	23.36±3.16**
Model	-	0.87±0.15	68.26±3.63	19.34±2.57	38.43±3.32	42.65±3.32
Captopril	0.1	0.43±0.11**	83.15±8.32	9.27±1.87**	21.32±3.41**	33.48±2.56
DNE-L	1.3	0.81±0.21	70.57±7.31	14.22±2.53	33.13±4.13	39.46±3.23
DNE-M	2.6	0.67±0.25	72.34±7.24	12.34±2.28	26.27±3.53*	35.32±3.64
DNE-H	5.2	0.53±0.35	77.42±6.31	9.13±2.12**	22.37±3.16**	24.27±3.55**

*L, M and H represent low-, medium- and high-doses of DNE, respectively, (n = 10, *p < 0.05, **p < 0.05)*

oxygen species and nitric oxide are involved in the process. Free radicals induce lipid peroxidation which damages cell membranes and accelerates cell apoptosis. Physiological antioxidants neutralize these free radicals, and NO is a physiological vasodilator. However, high levels of NO can lead to free radical formation and result in serious neurotoxicity, thus damaging the tissues. The synthesis of NO requires NOS [17]. In this study, DNE significantly reversed the CHF-induced increases in MDA and NO levels, and also decreased CK and NOS activities. Thus DNE reduced the oxidative stress state brought about by CHF. However, DNE had no significant effect on the activity of SOD, suggesting the effect of DNE was not mediated via SOD.

CONCLUSION

The findings of this study has demonstrated that DNE appreciably ameliorates chronic congestive heart failure, most probably by mitigation of oxidative stress, and the recovery of left ventricular function. Thus, DNE may be a potential source of new drug(s) for treating chronic heart failure in future.

DECLARATIONS

Acknowledgement

None.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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